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Elevated depressive symptoms and compositional changes in LDL particles in middle-aged men

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Abstract Depression and cardiovascular disease (CVD) are closely associated, but the mechanisms underlying this connection are unclear. Regardless of the low cholesterol levels observed in depression, a small particle size of low-density lipoproteins (LDL), as well as elevated apolipoprotein B (ApoB) levels, are related to increased CVD risk, even when levels of LDL cholesterol are low. We examined the association between elevated depressive symptoms and compositional changes in serum LDL particles in a sample of 2,456 middle-aged Finnish men. Depressive symptoms were assessed with the 18-item Human Population Laboratory Depression Scale, and the study population was divided into two groups (elevated depressive symptoms, $n = 269$; non-depressed, $n = 2{,}187$). The levels of serum total cholesterol (TC), low- and high-density lipoprotein cholesterol (LDL-C, HDL-C), triglycerides (TG), and ApoB were determined. The LDL-C/ApoB ratio, a marker of compositional changes in LDL particle size, was calculated. The group with elevated depressive symptoms had lowered levels of serum TC ($P = 0.028$) and LDL-C ($P = 0.008$). No differences were observed in the LDL-C/ApoB ratio. The likelihood for belonging to the group with elevated depressive symptoms increased 10% for each 0.5 mmol/l decrease in the levels of TC ($P = 0.002$) or LDL-C ($P = 0.001$) in regression models adjusted for age, examination years, marital and socioeconomic status, energy expenditure, body mass index, CVD history, alcohol consumption, smoking, and the use of lipid-lowering, antidepressant and antipsychotic medications. Our findings suggest that greater small-particle LDL levels are not associated with depression, and are thus unlikely to underlie the association between cardiovascular risk and depression.

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Abbreviations

ApoB	Apolipoprotein B
BMI	Body mass index
CVD	Cardiovascular disease
CES-D	Center for Epidemiological Studies Depression Scale
CI	Confidence interval
HDL-C	High-density lipoprotein cholesterol
HPL	Human Population Laboratory
LDL-C	Low-density lipoprotein cholesterol
OR	Odds ratio
TC	Total cholesterol
TG	Triglycerides

Introduction

The two major conditions affecting public health, depression and cardiovascular disease (CVD), are closely associated, although the mechanisms underlying this connection are unclear [1]. Altered lipid levels have been observed in both conditions. However, while high levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are associated with cardiac morbidity, low TC and LDL-C levels have been observed in depression [2, 3]. Nevertheless, these opposite depression-related observations could be explained by lipid-related factors other than the conventional cholesterol parameters. For instance, a small LDL-C particle size and elevated apolipoprotein B (ApoB) levels, both related to increased CVD risk even when levels of LDL-C are low [4], could underlie the connection between depression and CVD. To the best of our knowledge, however, no population-based studies have explored the role of LDL-C particle size and ApoB in depression.

Previous investigations into the associations between lipid levels and depression have provided highly discrepant findings, and the differences in study populations as well as the lack of adjustment for several possible confounders may have further increased this discrepancy. Regardless of the observed inconsistency, however, Shin and co-workers [5] concluded in their recent meta-analysis that the findings regarding an inverse association between TC levels and depressive symptoms appear to be convincing. No other lipid fractions presented such a reliable association. Nevertheless, the total number of investigations was fairly small for LDL-C and high-density lipoprotein cholesterol (HDL-C), leading to limitations in the analyses. Future investigations were recommended to focus on the roles of these less well-examined lipids in depression. Furthermore, the association between triglycerides (TG) and depressive symptomatology, previously observed to be discrepant, was not evaluated in the meta-analysis. Some studies have detected no association between TG and depression in men [3, 6, 7], while some mixed-gender samples have observed higher TG levels in depressed subjects [8].

In order to examine the role of LDL-C particle size and ApoB in depression, and to clarify the roles of LDL-C, HDL-C and TG, we investigated the relationship between depressive symptomatology and the levels of serum lipids and lipoproteins in a sample of 2,456 Finnish middle-aged men.

Methods

The Kuopio Ischemic Heart Disease Risk Factor Study was a population-based study of risk factors for ischemic heart disease and other outcomes among middle-aged men in the Kuopio region of eastern Finland [9]. A total of 2,682 participants (participation rate 82.9%) aged 42–60 years were recruited for the baseline examination, which occurred between March 1984 and December 1989. Data were incomplete for 226 participants; thus, complete data were available for 2,456 men. All participants provided written informed consent after full explanation of the study, and the study protocol was approved by the Research Ethics Committee of the University of Kuopio.

Assessment of depressive symptoms

Depressive symptoms were assessed with the 18-item Human Population Laboratory Depression Scale (HPL Depression Scale) [10]. The scale consists of items dealing with mood disturbance, a negative self-concept, loss of energy, problems with eating and sleeping, trouble with concentration, and psychomotor agitation. It was developed especially for screening general population samples, and it also conceptually resembles other brief symptom checklists such as the Center for Epidemiological Studies Depression Scale (CES-D) [11, 12]. The HPL Depression score is generated by assigning one point for each true or false answer that is indicative of depression (range 0–18). In some items, "often" or "never" responses, whichever appropriate, were calculated as one point. A cut-off score of five or more has earlier been used to define elevated depressive symptoms [10, 12, 13], and thus we applied the same cut-off point. Those who scored five or more were considered to have elevated depressive symptoms ($n = 269$, 10.9% of participants). Poor appetite as a covariate was derived from the HPL Depression Scale.

Socioeconomic factors, illness history and medications

Participants also completed questionnaires relating to their sociodemographic background, somatic and psychiatric medications and history of physical illnesses, including CVD. Marital status was reported as a two-class variable (married or living with a partner vs. living alone). A positive CVD history was coded based on the following criteria: first, all subjects had at least one of the following physician-diagnosed conditions: myocardial infarction, angina pectoris, other coronary conditions, cardiomyopathy, cardiac insufficiency or stroke. Second, all also used nitrates at least once per week, and had angina pectoris according to the World Health Organization angina pectoris questionnaire (the Rose Angina Questionnaire, RQ), a validated instrument to assess symptoms of typical angina pectoris in the general population [14, 15]. A variety of indicators of adulthood socioeconomic status were available, including current income, current and previous occupations, the highest level of education, the perception of financial security and housing tenure. In addition, an index of material living conditions

was created by summing the number of material possessions (e.g., dishwasher, car, summer cottage) from a list of 12. The variable "adulthood socioeconomic status" was formed from these indicators [16–18].

Smoking and alcohol consumption

The current number of cigarettes, cigars and pipefuls of tobacco smoked daily and the duration of regular smoking in years were recorded using a self-administered questionnaire. The number of years smoked was defined as the sum of the years of smoking, whether it had occurred continuously or during several periods. The lifelong exposure to smoking (pack years) was estimated as the product of years smoked and the number of tobacco products smoked daily at the time of the examination, or for ex-smokers at the time when they had last smoked. Alcohol consumption (g/wk) was assessed with a structured quantity-frequency method using the Nordic Alcohol Consumption Inventory for drinking behaviour over the previous 12 months [19].

Physical activity

Physical activity was assessed using the 12-month Physical Activity Questionnaire [20, 21]. The checklist included the most common physical activities of middle-aged men, for example walking, jogging, bicycling, swimming, and ball games. The subjects were asked to record the frequency, average duration, and intensity of each activity performed. A trained nurse checked and completed the questionnaire during an interview. The energy expenditure from physical activity was expressed as kcal per day.

Laboratory measurements

The weight and height of the participants were measured and the body mass index (BMI, kg/m^2) was calculated. The subjects came to the Research Institute of Public Health for venous blood sampling between 8 and 10 am. They had been instructed to abstain from alcohol for the previous 3 days, and from smoking and eating for 12 h before the laboratory testing. After a 30-min rest in a supine position, blood samples were drawn by venipuncture and collected into vacuum tubes (Venoject; Terumo, Leuven, Belgium) that contained ethylenediamine tetraacetic acid (EDTA) and placed on an ice-bath. No tourniquet was used. Plasma was separated by centrifugation for 15 min at +4°C (3,500 g) and was kept in an ice-bath before further handling. Lipoprotein fractionation was started on the day of blood collection.

Measurements of serum lipid and lipoprotein concentrations have been thoroughly described elsewhere [22]. In brief, lipoproteins were separated from fresh serum samples by combined ultracentrifugation and precipitation. The serum TC (reference value <5.0 mmol/l), HDL-C (reference value >1.0 mmol/l), LDL-C (reference value <3.0 mmol/l), and triglyceride (TG) (reference value <2.0 mmol/l) concentrations were measured enzymatically with the use of an autoanalyzer (Kone Specific, Kone Instruments, Espoo, Finland). Further, ApoB levels were determined by an immunoturbidimetric method (Kone Oy, Espoo, Finland). We also calculated the LDL-C/ApoB ratio, a marker of compositional LDL changes and an estimate of altered LDL particle size [23].

Statistics

The group differences between the participants with elevated depressive symptoms ($n = 269$) and the rest of the cohort ($n = 2{,}187$) were examined using the Mann–Whitney U-test for continuous variables, and the χ^2 test and Fisher's exact test for categorical variables. The non-parametric Mann–Whitney U-test was used due to the skewed distribution of the variables.

The lipid variables exhibiting significant group differences ($P < 0.05$) were further tested with logistic regression modelling. The likelihood (odds ratio, OR; 95% confidence interval, CI) for belonging to the group with elevated depressive symptoms was examined in a model adjusted for age, examination years, marital status, adulthood socioeconomic status, energy expenditure, BMI, CVD history, alcohol consumption, smoking, and the use of lipid-lowering, antidepressant and antipsychotic medications. Examination years (all except the first year in order to form a dummy variable) were included in the regression model as technical covariates in order to control for the possible bias created by the long 6-year period of baseline data collection. The continuous measures of the examined lipid variables were inserted separately into the regression model due to their high intercorrelations (Model 1: TC; Model 2: LDL-C).

Results

The characteristics of the study population are presented in Table 1. The group with elevated depressive symptoms reported more living alone and smoking, a higher alcohol consumption, an appetite decrease and CVD history, and had a lower level of physical activity. Furthermore, they used more antidepressant and antipsychotic medications. No differences were observed in the LDL-C/ApoB ratio between the depressed and other participants. None of the participants in the group with elevated depressive symptomatology used lipid-lowering medication. Nevertheless, they had lower levels of TC and LDL-C.

Table 1 Characteristics of the study sample

	Elevated depressive symptoms ($n = 269$)	Non-depressed ($n = 2,187$)	Test statistics*	P value
Age, years	53.49 (4.59)	53.01 (5.10)	$Z = -1.52$	0.128[a]
HPL depression scale scores	6.48 (1.86)	1.32 (1.28)	$Z = -27.49$	<0.001[a]
Married or living with a partner, *n* (%)	219 (81.4)	1,912 (87.4)	$\chi^2 = 7.54$	0.006[b]
Baseline examination performed, *n* (%)				
1985	52 (10.7)	434 (89.3)	$\chi^2 = 0.04$	0.842[b]
1986	51 (12.0)	375 (88.0)	$\chi^2 = 0.55$	0.459[b]
1987	44 (10.3)	382 (89.7)	$\chi^2 = 0.21$	0.650[b]
1988	31 (9.3)	302 (90.7)	$\chi^2 = 1.07$	0.302[b]
1989	52 (13.0)	348 (87.0)	$\chi^2 = 2.05$	0.152[b]
Length of education, years	8.62 (3.52)	8.63 (3.40)	$Z = -0.12$	0.901[a]
CVD history, *n* (%)	159 (59.1)	771 (35.3)	$\chi^2 = 57.9$	<0.001[b]
Lipid-lowering medication, *n* (%)	0 (0)	12 (0.5)	–	0.384[c]
Antidepressant medication, *n* (%)	21 (7.8)	10 (0.5)	–	<0.001[c]
Antipsychotic medication, *n* (%)	18 (6.7)	26 (1.2)	–	<0.001[c]
Smoking, pack years	11.22 (19.69)	7.99 (16.14)	$Z = -2.46$	0.014[a]
Alcohol consumption (g/week)	95.80 (138.58)	73.55 (137.06)	$Z = -2.05$	0.040[a]
Poor appetite, *n* (%)	53 (19.7)	78 (3.6)	$\chi^2 = 123.60$	<0.001[b]
Energy expenditure, kcal/d	137.33 (196.68)	141.23 (172.75)	$Z = -2.36$	0.018[a]
Body mass index, kg/m^2	26.93 (3.84)	26.88 (3.49)	$Z = -0.74$	0.461[a]
Total cholesterol (mmol/l)	5.77 (1.03)	5.93 (1.09)	$Z = -2.19$	0.028[a]
LDL-C (mmol/l)	3.88 (0.94)	4.06 (1.03)	$Z = -2.67$	0.008[a]
HDL-C (mmol/l)	1.30 (0.31)	1.29 (0.30)	$Z = -0.08$	0.934[a]
Triglycerides (mmol/l)	1.35 (0.84)	1.30 (0.83)	$Z = -0.49$	0.622[a]
ApoB (g/l)	1.01 (0.23)	1.04 (0.25)	$Z = -1.75$	0.079[a]
LDL-C/ApoB	3.90 (0.60)	3.96 (0.73)	$Z = -1.10$	0.272[a]

Values are means (±SD) unless otherwise stated

ApoB Apolipoprotein B, *CVD* cardiovascular disease, *HDL-C* high-density lipoprotein cholesterol, *HPL* human population laboratory, *LDL-C* low-density lipoprotein cholesterol, *SD* standard deviation

* Presented where applicable

[a] Mann–Whitney U-test

[b] χ^2 test

[c] Fisher's exact test

In logistic regression modelling, the likelihood of belonging to the elevated depressive symptoms group increased by 10% for each 0.5 mmol/l decrease in the levels of TC (OR 1.11, 95% CI 1.04–1.18, $P = 0.002$) or LDL-C (OR 1.12, 95% CI 1.04–1.19, $P = 0.001$). The history of CVD was independently associated with depression, regardless of the tested lipid variable (Table 2).

Discussion

Principal findings

We observed lower levels of TC and LDL-C, but no alterations in the LDL-C/ApoB ratio or ApoB levels in the group with elevated depressive symptomatology. The risk of belonging to this group increased by 10% for each 0.5 mmol/l decrease in the levels of either TC or LDL-C.

Comparison with previous studies

Our data are consistent with previous investigations in showing pronounced CVD morbidity in depression [1]. Increased levels of CVD, however, have also been associated with a small LDL-C particle size and high ApoB levels [4, 24]. Nevertheless, the LDL-C/ApoB ratio, an estimate of LDL particle size, and ApoB levels presented no associations with depression in our data. Thus, the present findings suggest that a small LDL-C particle size

Table 2 Odds ratios (95% confidence intervals) for the likelihood of belonging to the group with elevated depressive symptoms in logistic regression analysis

	OR	95% CI	*P*
Model 1			
Age	0.99	0.96–1.02	0.493
Married or living with a partner	0.64	0.45–0.92	0.014
Examination year			
1985	1.22	0.77–1.93	0.410
1986	1.49	0.93–2.38	0.094
1987	1.17	0.72–1.92	0.525
1988	1.16	0.68–1.98	0.577
1989	1.61	1.00–2.58	0.049
High socioeconomic status	1.06	1.02–1.10	0.001
High energy expenditure	1.00	1.00–1.00	0.610
High body mass index	0.98	0.95–1.02	0.391
History of cardiovascular disease (yes)	2.64	2.00–3.48	<0.001
Smoking (high number of pack years)	1.00	0.99–1.01	0.812
Alcohol use (high)	1.00	1.00–1.00	0.106
Lipid-lowering medication (yes)	0.00	0.00–	1.00
Antidepressant medication (yes)	14.9	6.45–34.5	<0.001
Antipsychotic medication (yes)	2.92	1.39–6.13	0.005
High TC[a]	1.11	1.04–1.18	0.002
Model 2			
High LDL-C[a]	1.12	1.04–1.19	0.001

HDL-C high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglycerides

[a] The likelihood for each 0.5 mmol/l decrease in the level of the examined lipid covariate

and high ApoB levels do not modify the increased depression-related CVD risk in middle-aged men.

In their recently published meta-analysis, Shin et al. [5] reported that TC levels were inversely associated with depression. Our findings are in line with these observations. The levels of LDL-C, however, presented no association with depression in the same meta-analysis [5]. The total number of subjects in all studies investigating the LDL-C levels was only 6176, whereas in the TC studies the respective figure was as high as 45,098. The subject number of the present study essentially adds to the total number of subjects in LDL-C investigations, and also supports the previous findings of an inverse association between depression and LDL-C [3, 6, 25].

A large Finnish prospective study on 29,133 male smokers showed an inverse association between TC and depressive symptoms [2]. Our findings demonstrate that, regardless of smoking habits, the same association remains observable in men. Moreover, our group has previously observed low HDL-C levels, but no alterations in TC or LDL-C, in a mixed-gender sample of same-area general population subjects with a diagnosis of major depressive disorder, and a recorded 7-year history of depressive symptoms [26]. Since the inverse association between TC levels and depression has been observable regardless of gender [5], the different gender distribution of these two investigations is unlikely to affect the observed discrepancy. Nevertheless, the baseline data collection for the present study took place more than 10 years earlier than that of the other study from the same area, and thus time-related dietary or life-style alterations could explain these discrepant observations. We observed a prevalence of 12% for elevated depressive symptoms, which is slightly higher than the previously observed 7.4% prevalence of major depressive disorder in men in Finland [27].

Possible mechanisms

The most well-known biological explanation for the effect of low cholesterol levels on depression is the theory of Engelberg [28], who suggested that low cell-membrane cholesterol levels lead to decreased serotonergic transmission. This hypothesis was further supported by neuroendocrine challenge testing that showed a positive association between serotonergic functions and cholesterol levels in men, but not in women [29]. Both of the previous hypotheses suggest that low cholesterol levels lead to depression. However, inverse causal relationships also need to be considered. A depression-related poor appetite may lead to lowered cholesterol levels. In our sample, however, adjustment for poor appetite did not alter the findings, although the elevated depressive symptomatology group reported a poor appetite more often than the non-depressed group.

Strengths and limitations

To the best of our knowledge, no previous investigations have examined the alterations in LDL particle size estimates in depression. The main strength of this study was the large, representative sample of middle-aged Finnish men. In addition, we were able to adjust for several major confounding factors such as appetite, BMI, CVD history, physical activity, socioeconomic factors, and relevant psychiatric and somatic medications. Due to the early period of data collection, i.e., 1984–1989, very few individuals in the study sample used lipid-lowering medications. This can be considered as a strength, because it minimises the potential confounding effect of these medications on our findings. However, there are some limitations in this study. First, the sample comprised exclusively men, and thus these findings cannot be generalized to women. Second, due to the cross-sectional nature of the

present study, we are unable to draw causal conclusions on the connections between depressive symptomatology and serum lipids. Third, due to the large sample size, we were unable to perform diagnostic psychiatric interviews for the study subjects. The assessment of mood was, however, performed with a scale specifically designed for epidemiological studies [11, 12]. In addition, the HPL depression scale is highly correlated with the well-established Beck Depression Inventory [10, 30].

Conclusions

Our findings suggest that greater levels of small-particle LDL, a factor predisposing to coronary heart disease, are not associated with depression. Thus, LDL particle size alterations may be unlikely to explain the association between cardiovascular risk and depression. Since the observed depression-related low levels of TC and LDL-C may be indicators of serotonergic disturbances, monitoring both low and high cholesterol levels may be warranted in all health care settings.

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